Towards understanding interchangeability of generic drugs

Valorisation Addendum

RELEVANCE

Generic drugs and the concept of bioequivalence for registration of a generic drug have been used more than 50 years. Discussions with respect of interchangeability (i.e. therapeutic equivalence) of the generic drugs with the brand-name drug are still ongoing. Although the trust of using generic drugs in practice increased in the past 10 to 20 years, some issues and concerns of using generic drugs are still reported in public media and literature. In this dissertation, interchangeability of generic drugs has been investigated with new approaches, and the findings and conclusions are highly relevant to societies worldwide.

REGULATORY SCIENCE AND INNOVATION

In the light of regulatory science, the dissertation serves the objectives of the subject that "regulatory science is the scientific domain targeting the development of new instruments, standards and methods to optimally facilitate the evaluation of the efficacy, risks and quality of medicinal products. Knowledge development focuses on both new instruments and their application." In Chapter 3, the results showed that the observed difference in drug exposure after switching to a generic drug was related to intrasubject variability of the active substance, rather than formulation-dependent variation in drug exposure. It indirectly demonstrated that the currently required average bioequivalence approach for registration of a generic drug by regulatory authorities is reliable and also sufficiently to ensure the interchangeability of treatment between generic and the brand-name drug in individual patients. The study also contributes to the discussion for replacing the average bioequivalence approach by individual/population bioequivalence approaches, and in fact supports the action of termination by FDA for replacing the traditional average bioequivalence approach. Furthermore, the studies in Chapter 4 and Chapter 7 were conducted with the purpose of reviewing the regulatory system, further understanding the possible influence of regulatory actions on the interchangeability of generic drugs. The study results showed currently the influence is limited, however the situation may to change along with the increase of the number of post-marketing (quality) variations and revision of guidelines in the future. Thus, the methods applied in these studies can be utilized when a regular check for the similar concerns is needed in the future.

In addition, considering the core responsibility of medicine regulatory authorities, i.e. to ensure the effectiveness and safety of the medicines in patients, investigations of generic-generic drug interchangeability (Chapter 5 and 6) is highly relevant and has a unique contribution in this field. First, generic-generic drug interchange happens in clinical practice, however currently no legislation is in place to require a demonstration of bioequivalence between a generic drug to the rest of marketed generic drugs during

its registration process. Over time, when more and more generic drugs on the market, the occurrence of generic-generic drug interchange will be more frequent. Therefore, it is necessary to have an investigation on this potential issue, understanding the possible consequence, in order to provide rational recommendations for regulatory actions.

Overall, this dissertation does not only provide evidence to resolve the regulatory system related concerns of generic drugs from a regulatory point of views, but also the methods can be used in the future to support regulatory actions by the authorities. In addition, regulatory science itself is an innovative discipline/subject. The majority of the methods applied in the investigations of this dissertation are innovative and can be applied later on. To our knowledge, the clinical trial with gabapentin drugs (Chapter 5) was the first study to investigate the interchangeability between generic drugs in vivo.

Social impact (patients and healthy professionals)

This dissertation has a great impact on society and economics. In clinical practice, patients may hesitate to take medicines when the treatment is changed from the brand-name drug to a generic drug, or from the generic drug to other generic drug. Sometimes, doctors also hesitate to prescribe generic drugs. If there is any complaint regarding effectiveness or safety from the patients who switched between generic drugs, the doctors are likely to ascribe the issue to generic drugs. In turn patients are likely to be switched back to the brand-name drug, which increases the costs substantially. This dissertation concluded that the generic drugs can be trusted. The conclusion is expected to have a positive influence on the prescription of generic drugs, to avoid unnecessary worrying.

Economic impact

Indirectly the financial burden of the healthcare system may be reduced. Generic drugs are much cheaper than the brand-name drugs (10% of the price of the brand-name drugs). Unnecessary remaining in use of the brand-name drugs brings financial burden to the health system. From that point of view, increasing the trust of using generic drugs can prevent unnecessary switch-back rate, and increase the prescription of generic drugs, which in turn reduce the burden in the health system.

Academic contributions

In addition, this dissertation has an obvious contribution to the academic world. Four chapters have been published in scientific journals with high impact factors. The publication of Chapter 3 has been reported as news " Overstappen op generiek niet onveilig " in *Nederlands Tijdschrift voor Geneeskunde* (Dutch Journal of Medicines). Following this piece of news, we were an invited to publish a summary of the article in *Pharma-*

ceutisch Weekblad (Journal of the pharmaceutical association), i.e. " Voor- en nadelen generiek middel en spécialité gelijk " (PW26, 2016). When Chapter 5 was published in the journal of *Clinical Pharmacology and Therapeutics*, in the same issue of the journal the US FDA published a perspectives paper "*Confidence in Generic Drug Substitution*" (R. Lionberger, 2013) referring to our article.

Overall, the dissertation provides significant contributions to societies. The conclusions and results of the conducted investigations are not only applicable for drug regulatory authorities, but also to patients and healthcare professionals. Indirectly it reduces the financial burden of the healthcare system and also promote better communications between the stakeholders.